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Original Article

Therapeutic effects of arsenic trioxide plus all-trans retinoic acid on acute promyelocytic leukemia

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Abstract: Objective: The aim of the current study was to observe the therapeutic effects of arsenic trioxide (ATO) plus all-trans retinoic acid (ATRA) on acute promyelocytic leukemia. Methods: A total of 92 patients with acute promyelocytic leukemia were selected and assigned into the control group (44 patients that received ATRA) and observation group (48 patients that received ATRA plus ATO). Patients were observed for the required treatment time to achieve complete remission during induction chemotherapy. They were detected for negative conversation of the PML-RARa gene after treatment using gene detection. Total amount of platelet and plasma transfusion during chemotherapy, incidence of adverse reactions after chemotherapy, overall survival (OS), and disease-free survival (DFS) were recorded. Results: The time required for first complete remission in the observation group was shorter than that in the control group. The negative conversion rate of the PML-RARa gene was higher in the observation group than in the control group. The volume of plasma and platelet transfusion in the observation group was less than that of the control group, with statistical differences (all $P < 0.05$). Cases of complete remission, as well as 5-year OS and DFS, were significantly less in patients with high white blood cell counts and/or low platelet counts, detected at initial diagnosis, than in patients with lower white blood cell counts and/or low platelet counts at initial diagnosis. There were no differences in OS between the two groups within 5 years ($P > 0.05$), but the DFS of the observation group was longer than that of the control group, with statistical differences ($P < 0.05$). Conclusion: ATRA plus ATO for treatment of acute promyelocytic leukemia can shorten remission times, increase the negative conversion rate of the PML-RARa gene, and improve the DFS of patients. Moreover, high white blood cell counts, along with low platelet counts, were shown to be important markers of poor prognosis.

Keywords: Arsenic trioxide, all-trans retinoic acid, acute promyelocytic leukemia, therapeutic effect, observation

Introduction

Acute promyelocytic leukemia (APL) is a special type of acute myelogenous leukemia, with an incidence of 10% to 15%. It is commonly seen in adults. The disease is special because it involves specific genetic cytological changes. Fusion of promyelocytic leukemia genes of chromosome 15 and retinoic acid receptor a of chromosome 17 (PML-RARa) eventually lead to occurrence of this disease [1]. Patients with APL manifest life-threatening clinical symptoms, such as bleeding and disseminated intravascular coagulation [2]. Fortunately, prognosis can be improved with the use of precise gene target therapy because of the high specificity of genetic markers [3]. Gene target therapy introduced all-trans retinoic acid (ATRA) to treatment of APL, decreasing early mortality significantly and prolonging the survival period of patients [4]. Furthermore, incidence of lethal infections, massive intracranial hemorrhages, and disseminated intravascular coagulation decreased significantly in the ATRA treatment process. However, the use of ATRA alone could result in severe myelosuppression and drug resistance [5]. Although patients had complete remission of symptoms, the negative conversion rate of the fusion gene PML-RARa was only about 20%, resulting in many recurrences after complete remission. A previous study reported recurrence rates of 50% to 68% after treatment with ATRA alone [6].

Therefore, methods of combining other drugs based with ATRA to reduce recurrence rates

have become a clinical concern. During the exploration process, ATRA plus anthracycline-based chemotherapy has been applied, showing decreased recurrence rates and decreased incidence of hyperleukocytosis, compared with ATRA alone [7]. However, there were still about 5%-30% of patients that relapsed [8]. Arsenic trioxide (ATO) brings new hope to patients with APL. It can achieve 70%-80% complete remission, with 80% achieving remission on the molecular level. This is a clear advantage, compared with ATRA [9]. Therefore, regimens of ATRA plus ATO began to be used in clinic. Two randomized controlled trials compared ATRA plus ATO and ATRA plus other chemotherapeutic drugs. They found that ATRA combined with ATO improved therapeutic effects, significantly [10, 11]. The regimen has been recommended in the guide of APL treatment, but it is not recommended for high-risk patients [12]. Previous studies have found that, during treatment with ATRA plus ATO, ATO has certain toxicity. It can lead to adverse reactions, such as leucocytosis and toxicity in the heart and liver [13, 14]. Thus, efficacy and safety levels of ATRA plus ATO should be investigated.

Materials and methods

General data

A total of 92 patients with APL, admitted to the Department of Hematology of Harbin Medical University, from November 2008 to November 2013, were enrolled. Patients included 51 males and 41 females, aged 19-64 years (mean, 38.1 ± 8.7 years). Forty-eight patients were assigned to the observation group and received ATRA plus ATO, including 24 males and 24 females, with an average age of 38.2 ± 10.0 years. A total of 44 patients were assigned to the control group and received ARTA, including 27 males and 17 females, with an average age of 38.1 ± 7.1 years. Both groups were followed-up for 5 years. The present study was approved by the Ethics Committee of Harbin Medical University and informed consent was obtained from all included patients.

Inclusion & exclusion criteria and grouping

Inclusion criteria: Patients with APL seeking initial treatment; Aged 18 to 65 years; Diagnosed with type M3 according to the FAB bone marrow diagnostic criteria proposed in 1995 [15]; Had a positive PML-RARa gene.

Exclusion criteria: Patients that had received the same treatment before; High-risk patients; Pregnant or in lactation; Had other severe cardiopulmonary diseases and were not suitable for the operation; Had other malignant tumors; Were not applicable for follow-ups or not cooperative with the protocol; Had other types of genetic diseases.

Patients in each group were further divided into two subgroups, according to white blood counts (WBC) and platelet (PLT) counts, at the initial visit. Patients with WBC $\leq 10*10^9$/L and WBC > $10*10^9$/L were assigned into two different WBC subgroups. Patients with PLT < $40*10^9$/L and PLT $\geq 40*10^9$/L were assigned into two different PLT subgroups.

Chemotherapy

Patients in the control group were given oral ATRA (Shanghai Great Wall, China) at a dose of 25 mg/m^2/d, three times a day. Patients in the observation group were given the same dose of ATRA plus intravenous ATO (Beijing Shuanglu, China), at 0.16 mg/kg/d once a day. When the two groups of patients achieved complete remission with the use of the above treatment regimens, treatment was consolidated with daunorubicin (Shenzhen Wanle, China) for 2 courses. For each course, patients were treated with 3-5 intravenous drips at a dose of 1 mg/kg. The interval between the two courses was 3 weeks. The maintenance treatment regimen was as follows. For the control group, chemotherapy consisted of the alternant use of ATRA and daunorubicin. The observation group was treated with the alternant use of ATRA, ATO, and daunorubicin. During the entire process, active silver-ion antibacterial solution (Xi'an Kangwang, China) was used for gargling, and boric acid powder (Shanghai Winguide Huangpu, China) was used for hip baths. These were routinely administered according to patient conditions and confirmed diagnosis. Infusion of pheresis PLT was performed to maintain the PLT above $30*10^9$/L. Infusion of suspended red blood cells was conducted to maintain hemoglobin > 80 g/L. All patients were regularly monitored for coagulation function. Infusions with fresh frozen plasma, cryoprecipitate, and fibrinogen were given for patients with coagulation dysfunction to maintain fibrinogen above 1.5 g/L. Moreover, regular reviews were conducted. Patients with infections were immediately underwent secretions

Table 1. Comparison of baseline data

Item	Observation group (n = 48)	Control group (n = 44)	χ^2/t	P
Sex (male:female)	24:24	27:17	1.200	0.273
Age (year)	38.2 ± 10.0	38.1 ± 7.1	0.043	0.966
Laboratory parameters				
White blood count (*10^9/L)	12.70 ± 2.03	13.10 ± 1.55	1.053	0.295
Platelet count (*10^9/L)	43.73 ± 13.79	45.43 ± 13.76	0.592	0.555
Hemoglobin (g/L)	69.85 ± 10.35	69.25 ± 9.97	0.285	0.776
Rate of myeloid promyelocyte (%)	62.73 ± 10.26	62.26 ± 9.93	0.219	0.827

and blood culturing. An adequate amount of broad-spectrum antibiotics was then administered. Use of antibiotics was adjusted according to experiments on bacterial resistance.

Outcome measures

There were 4 main outcome measures. 1) Time required for complete remission (CR) in patients undergoing induction chemotherapy. It was defined as complete remission when myeloblasts + promyelocytes ≤ 5%, hemoglobin greater than 100 g/L (male) or 90 g/L (female), absolute value of neutrophils greater than 1.5*10^9/L, without white blood cells, PLT greater than 100*10^9/L, and if there were no clinical manifestations, such as anemia, bleeding, infections, and leukocyte infiltration; 2) Negative conversion rate of the PML-RARa gene detected by reverse-transcription PCR assay (provided by CapitalBio, China); 3) Total amount of PLT and plasma transfused during the entire chemotherapy was recorded; 4) Presence of adverse reactions after chemotherapy was recorded. If the patient had one of the following symptoms and signs: dyspnea, unexplained fever, weight gain, peripheral edema, unexplained drop of blood pressure, acute renal failure, congestive heart failure, and especially pleural and pericardial effusion, then retinoic acid syndrome was suspected. Thus, the amount of ATRA was reduced or discontinued (for patients with severe symptoms). Additionally, intravenous dexamethasone (Henan Lingrui, China) was given to relieve the symptoms above. Treatment was continued after symptom remission. Other symptomatic treatments were as follows. Azastron (Zhejiang Wanxiang, China) and tropisetron (Beijing Huasu, China) were given to stop vomiting. Acid-inhibitory drugs, such as pantoprazole (Zhejiang Huadong, China) and omeprazole (Yangtze River Pharmaceutical Group, China), were prescribed and liver protection was given for patients with relevant symptoms. Neurotrophic drugs, such as intravenous mecobalamine (Hainan Star, China), were given to patients with nerve injuries. Immunosuppressive treatment of intravenous dexamethasone and medicinal paste was given to patients with rashes.

Secondary outcome measures were as follows. Outpatient follow-ups were performed for all patients for a period of 5 years. If patients died during the 5 years, the death date was regarded as cut-off time. Overall survival (OS) was from complete remission to the cut-off time. Disease-free survival (DFS) was from complete remission to recurrence or the cut-off time. Recurrence rate was the ratio of the number of relapsed patients to the total number of follow-up cases.

Statistical analyses

Statistical analyses were performed using SPSS 22.0 software. Continuous variables are expressed as mean ± standard deviation ($\bar{x}$ ± sd). Data conforming to normal distribution and homogeneity of variance were compared, before and after treatment, within groups with the use of paired t-tests. Data not conforming to normal distribution and homogeneity of variance were compared with the use of rank sum tests. Comparisons between groups were performed using independent sample t-tests. Count data are expressed as number/percentage (n/%) and were processed using Pearson's Chi-squared tests, expressed as χ^2. Survival analysis was performed using Kaplan-Meier analysis and log-rank tests. Differences are statistically significant at $P < 0.05$.

Table 2. Comparison of clinical efficacy

Item	Observation group (n = 48)	Control group (n = 44)	χ^2/t	P
Number of CR	40	38	0.163	0.686
Time required for the first CR (day)	28.43 ± 6.05	33.98 ± 6.72	5.035	< 0.001
Negative conversion rate of PML-RARa gene (%)	48 (100%)	36 (81.82%)	9.558	0.002
Plasma infusion (mL)	830.20 ± 75.40	942.67 ± 66.96	7.577	< 0.001
Platelet infusion (U)	33.18 ± 8.84	52.35 ± 11.98	8.665	< 0.001

Note: CR = complete remission; PML-RARa = promyelocytic leukemia retinoic acid receptor a of chromosome 17.

Table 3. Relationships between WBC at initial visit and CR, OS, and DFS

Item	Observation group	Control group	Total number
Number of CR			
WBC ≤ $10*10^9$/L	28 (28/31)	25 (25/27)	53 (53/58)
WBC > $10*10^9$/L	9 (9/17)	10 (10/17)	19 (19/34)
χ^2	8.685	7.311	15.875
P	0.003	0.007	< 0.001
Number of 5-years OS			
WBC ≤ $10*10^9$/L	29 (29/31)	25 (25/27)	54 (54/58)
WBC > $10*10^9$/L	9 (9/17)	10 (10/17)	18 (18/34)
χ^2	10.977	9.339	20.171
P	0.001	0.002	< 0.001
Number of 5-year DFS			
WBC ≤ $10*10^9$/L	28 (28/31)	24 (24/27)	52 (52/58)
WBC > $10*10^9$/L	8 (8/17)	8 (8/17)	16 (16/34)
χ^2	10.960	9.203	20.171
P	0.001	0.002	< 0.001

Note: CR = complete remission, WBC = white blood count, OS = overall survival, DFS = disease-free survival.

Results

Comparison of baseline data

There were no differences in gender, age, risk levels, and laboratory parameters between the two groups (all P > 0.05). See **Table 1**.

Comparison of clinical efficacy

A total of 78 patients achieved CR in the two groups, with 40 in the observation group and 38 in the control group. Moreover, 72 patients had a 5-year OS. The time required for the first CR was shorter in the observation group than in the control group (P < 0.05). The negative conversion rate of the PML-RARa gene was higher in the observation group than in the control group (P < 0.05). The amount of plasma and PLT infusion was less in the observation group than in the control group (P < 0.05). See **Table 2**.

Relationship between WBC at initial visit and CR

Patients with a 5-year OS and DFS were 72 and 68, respectively. Patients with high WBC (> $10*10^9$/L) at initial visit showed a significantly smaller number of CR and 5-year OS and DFS than other patients (all P < 0.05). See **Table 3**.

Relationship between PLT count at initial visit and CR

Patients with low PLT (< $40*10^9$/L) at the initial visit showed a significantly smaller number of CR and 5-year OS and DFS than other patients (all P < 0.05). See **Table 4**.

Comparison of adverse reactions

A total of 33 patients in the observation group and 22 in the control group had adverse reactions. There were no statistical differences between the two groups (P > 0.05). See **Table 5**.

Comparison of 5-year OS

OS in the observation group was 117.65 months (95% CI: 114.45-120.84), longer than the 98.32 months (95% CI: 90.26-106.38) in the control group. However, there were no statistical differences (χ^2 = 3.848, P = 0.050). See **Figure 1**.

Comparison of 5-year DFS

DFS in the observation group was 116.50 months (95% CI: 112.66-120.34), longer than the 95.96 months (95% CI: 87.56-104.35) in the control group. Differences were statistically

Table 4. Relationships between PLT count at initial visit and CR, OS, and DFS

Item	Observation group	Control group	Total number
Number of CR			
PLT < 40*10^9/L	12 (12/18)	10 (10/15)	22 (22/33)
PLT ≥ 40*10^9/L	28 (28/30)	28 (28/29)	56 (56/59)
χ^2	5.760	7.479	13.090
P	0.016	0.006	< 0.001
Number of 5-year OS			
PLT < 40*10^9/L	10 (10/18)	9 (9/15)	19 (19/33)
PLT ≥ 40*10^9/L	26 (26/30)	27 (27/29)	53 (53/59)
χ^2	5.807	7.283	12.941
P	0.016	0.007	< 0.001
Number of 5-year DFS			
PLT < 40*10^9/L	9 (9/18)	8 (8/15)	17 (17/33)
PLT ≥ 40*10^9/L	25 (25/30)	26 (26/29)	51 (51/59)
χ^2	6.050	7.427	13.388
P	0.014	0.006	< 0.001

Note: CR = complete remission, PLT = platelets, OS = overall survival, DFS = disease-free survival.

Table 5. Comparison of adverse reactions

Adverse reactions	Observation group	Control group	χ^2	P
Case	48	44	2.039	0.100
Bleeding or coagulation dysfunction	5 (10.42%)	7 (15.91%)	0.611	0.435
Differentiation syndrome	1 (2.08%)	2 (4.55%)	0.006	0.939
Cardiotoxicity	8 (16.67%)	0 (0.00%)	6.070	0.014
Elevated liver enzyme	7 (14.58%)	5 (11.36%)	0.210	0.674
Gastrointestinal symptoms	9 (18.75%)	8 (18.18%)	0.005	0.944
Nerve injury	2 (4.17%)	0 (0.00%)	0.427	0.514
Symptoms on skin and mucous	1 (2.08%)	0 (0.00%)	0.000	1.000
Total number (n, %)	33 (68.75%)	22 (50.00%)	1.008	0.067

significant between the two groups (χ^2 = 4.623, P = 0.032). See **Figure 2**.

Discussion

ATRA significantly reduces the risk of bleeding in APL patients. Hemorrhaging and disseminated intravascular coagulation are the main causes of death during the early stages of APL. Two multicenter studies found that CR rates, after ATRA treatment, reached 89.6%. Five-year OS rates of the control group and observation group were 83.9% and 86.1%, respectively [16, 17]. With the use of ATO, the combination of ATRA and ATO for APL has increased CR rates to greater than 90%. Of these, 80% achieved remission at the molecular level, indicating that combination of the two has obvious advantages, compared with ATRA alone [9, 18-20]. In the present study, the time required for the first CR was shorter in the observation group, treated with ATRA and ATO, than in the control group, treated with ATRA alone, The negative conversion rate of the PML-RARa gene in the observation group was 100%, higher than that of the control group, with statistical differences. As a result, volumes of PLT and plasma transfusion were fewer in the observation group than in the control group, with statistical differences.

In terms of factors affecting prognosis, two previous studies found that early death is associated with high WBC [21, 22]. Another study found that patients with middle or high-risk APL, namely WBC at 50*10^9/L, had an early mortality rate of 24%. Moreover, 3-year OS and DFS rates were 69% and 74%, respectively [23]. One study of PLT found that patients with low PLT (< 40*10^9/L), at the initial visit, had a significantly higher risk of recurrence than patients with higher PLT [24]. In this study, patients with high WBC and low PLT were found to have decreased CR rates, as well as 5-year OS and DFS rates.

The current study examined adverse reactions during the trial. ATO has certain toxicity. Thus, a certain number of clinical studies have reported its toxic side effects. These show different clinical manifestations, including hemorrhaging and coagulation disorders [25]. Mechanisms may be associated with decreased fibrinogen and elevated D-dimer [26, 27]. Another common symptom is differentiation syndrome, the

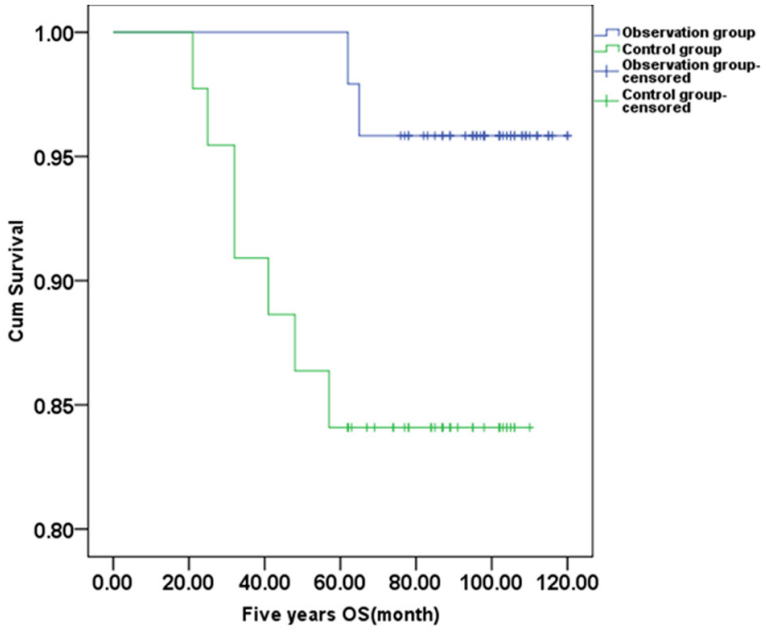

Figure 1. Comparison of 5-year OS. OS: overall survival.

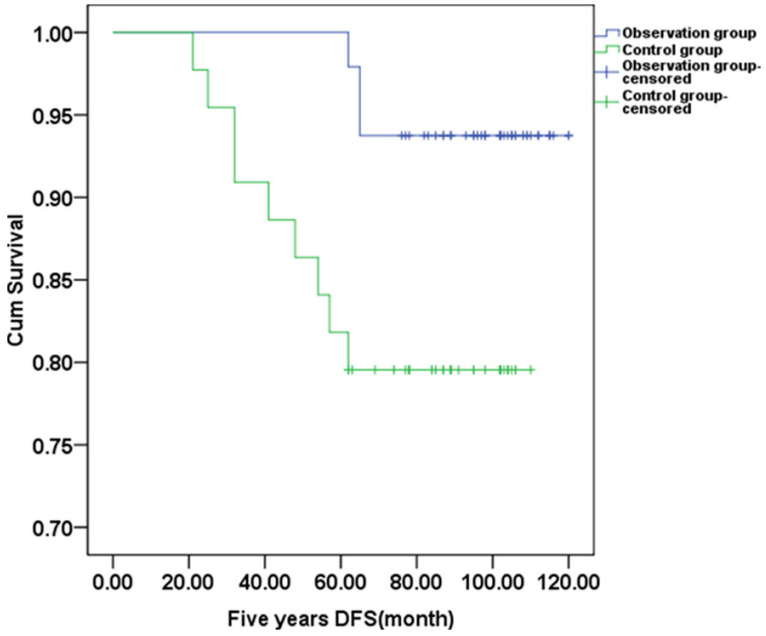

Figure 2. Comparison of 5-year DFS. DFS: disease-free survival.

general term for retinoic acid syndrome caused by ATRA treatment or ATO treatment. A previous study found that incidence of this side effect was about 20% [28]. However, incidence in this study was lower than that in the above studies. The reason may be related to the small sample size and early intervention in the current study. A study of cardiotoxicity found that use of ATO was related to the redox of human body, which increased the activity of cytochrome P450, thereby damaging myocardial cells and causing cardiotoxicity [29]. Another study reported an incidence of 30% in patients receiving intravenous ATO [30]. In the current study, incidence of myocardial damage in the observation group (received ATO) was 16.67%, which was close to the results of above-mentioned studies. Hepatotoxicity is mainly caused by ATO oxidative stress damage to liver mitochondria. This leads to toxic side effects and promotes the death of hepatocytes [31]. In an animal experiment, arsenic was given to test rats. Mitochondrial reactive oxygen species in liver cells were formed due to arsenic, in a concentration-dependent manner, thereby causing damage to liver cells [32]. In the current study, incidence of liver function abnormalities was 14.58% in the observation group and 11.36% in the control group, possibly related to toxic side effects of chemotherapy medication. Gastrointestinal symptoms are common adverse reactions in chemotherapy. Incidence of gastrointestinal symptoms after ATO treatment is about 30%, with a small number of patients developing pancreatitis [33, 34]. Incidence of gastrointestinal symptoms was highest in the current study, in accord with previous results. Headaches are a symptom of neurotoxicity, which is rare in clinical practice. This is because ATO cannot pass the blood-brain barrier and is low in cerebrospinal fluid. There have been a few cases reported [35]. A few patients developed headaches in the current study, consistent with the above reports. Rashes are a toxic side effect of ATO on the skin and mucosa.

Mechanisms, however, remain unclear. It may be related to genetic polymorphisms [36]. A previous study reported one case of erythema multiforme. Symptoms were improved after using hormones and anti-allergic drugs, without stopping chemotherapy [37].

In terms of prognosis of patients, a previous study in Australia enrolled 124 patients with APL. Patients were treated with ATRA plus ATO. Three-year OS and DFS rates were 93.2% and 88.1%, respectively. Compared with a previous study in the same center, patients were not treated with ATO. Both DFS and recurrence-free survival were improved, but there were no significant differences in OS. Another study in the US was conducted, with the same treatment regimen adopted and a 5-year follow-up period. It was found that the OS and DFS were 94.0% and 90.0%, respectively, in accord with the results of the study in Australia [38]. Another study found that the use of ATRA or ATO alone after CR increased the risk of recurrence, affecting DFS and OS rates [39]. In the current study, two groups of patients were followed up for 5 years. DFS rates in the observation group using ATRA plus ATO were statistically better than those in the control group. However, OS rates of the two groups were not statistically different.

The current study was a retrospective study with a relatively small sample size. Therefore, further randomized controlled studies with larger sample sizes should be conducted, comparing the efficacy and prognosis of the two regimens thoroughly.

In conclusion, ATRA plus ATO for treatment of APL can shorten remission times, increase the negative conversion rate of PML-RARa gene, and improve DFS rates of patients. Moreover, high white blood cell counts and low platelet counts are important markers of poor prognosis.

Disclosure of conflict of interest

None.

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